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Prevention of exercise induced asthma by inhaled salmeterol xinafoate

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Abstract

The effect of inhaled salmeterol xinafoate, a long acting β_2 agonist, on exercise induced asthma was studied in a double blind, crossover, and placebo controlled trial. Thirteen asthmatic children with a fall of at least 15% in their forced expiratory volume in one second (FEV_1) after a standard exercise test on a motorised treadmill, on separate days performed the same test 1, 5, and 9 hours after a single dose of 50 μg salmeterol or placebo. FEV_1 was measured before treatment, and before and for 30 minutes after each exercise test. After placebo the number of children with exercise induced asthma was: 10 at 1 hour, 11 at 5 hours, and 12 at 9 hours. Salmeterol prevented exercise induced asthma in all 13 children studied, at 1, 5, and 9 hours. Mean maximum falls in FEV_1 after exercise were at 1 hour: salmeterol 2·7% and placebo 24·6%, 5 hours: salmeterol 5·3% and placebo 22·7%; and 9 hours: salmeterol 3·4% and placebo 26·6%. After salmeterol the mean increase in FEV_1 was 17·8% at 1 hour, 19·6% at 5 hours, and 19·2% at 9 hours. Inhaled salmeterol prevents exercise induced asthma and produces significant bronchodilatation for at least 9 hours.

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Exercise is a common problem for children with asthma, who tend to be more physically active than adults. Over 70% of asthmatic children studied with treadmill exercise tests have exercise induced asthma,[1 2] and 98% of children attending an asthma clinic complained of symptoms on exercise.[3]

The airway response to exercise is a measure of indirect bronchial responsiveness; the mechanism is not fully understood but probably involves bronchial smooth muscle cells, mast cells, and neurons[4 5] with the release of mediators.[5–7] This response to exercise has been used to assess the efficacy and duration of action of asthma treatments.[3] Inhaled β_2 adrenoceptor agonists are the most effective drugs for the prevention of exercise induced asthma when taken five to 15 minutes before exercise.[8–10] This protective effect, however, lasts for only two hours in the majority of asthmatics[7 8 11] and the duration varies widely.[8 12]

Salmeterol xinafoate is a long acting β_2 adrenoceptor agonist. It has a polar phenylethanolamine head which binds reversibly to the β_2 receptor.[13] In addition to this it has a long non-polar side chain which is thought to bind to the cell membrane adjacent to the β_2 receptor.[14] It has been shown to inhibit in vitro constriction of airway smooth muscle[15] and the release of mediators from mast cells.[13] It produces prolonged bronchodilatation in adult asthmatic patients.[14] The long duration of effect is attributed to an action of the long non-polar side chain. Salmeterol also ablates both the early and late bronchial reaction and the increase in bronchial responsiveness that follows allergen challenge.[16]

There are no published data on the effect of salmeterol in exercise induced asthma or of its use in children. Our aim was to study the effect of a single dose of inhaled salmeterol on exercise induced asthma in children. It has been shown in previous studies that the degree of bronchoconstriction after exercise is reproducible[1] and does not alter significantly with repetition, at intervals of greater than two hours, during the day.[3] We therefore investigated the response to exercise in a group of asthmatic children 1, 5, and 9 hours after a single morning dose of salmeterol. The study was placebo controlled because placebo has been shown to reduce significantly exercise induced asthma in up to 40% of children.[17]

Methods

TRIAL DESIGN

The study was double blind, randomised, crossover, and placebo controlled. Children attending the paediatric asthma clinic at King's College Hospital who gave a clear history of exercise induced cough or wheeze and who were proficient in spirometry, were recruited. The parents gave informed consent for their children to participate and the study was approved by the hospital ethical committee. We calculated from a previous study of exercise induced asthma in children[1] that to detect a 20% difference in the mean maximum fall in forced expiratory volume in one second (FEV_1) after exercise between salmeterol and placebo with 90% power at the 5% level we would require a sample size of 13 patients.

Each child attended the paediatric respiratory laboratory for an initial exercise test. All medication except inhaled steroids was stopped for at least 12 hours beforehand. FEV_1 was measured in a Jaeger Bodytest reverse plethysmograph, with a capacity of 800 litres, checked against a IL calibration syringe on each occasion. This system was used because many of the children were already familiar with it, the scale could be easily adjusted for different sized children, and for its convenience in making multiple recordings.

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If the baseline FEV_1 was greater than 60% of the mean predicted for the child's height[18] the exercise test was done. This consisted of continuous running on a motorised treadmill for two minutes at 5 degrees upward inclination and a speed of 2·5 kilometres per hour (kph), followed by six minutes at 10 degrees and 5 kph.

Heart rate was measured before and immediately after the running period and then FEV_1 was measured every three minutes for 15 minutes and every five minutes for a further 15 minutes. The maximum percentage fall in FEV_1 from baseline was calculated. Children who attained a pulse rate of at least 170 beats per minute (bpm) and had a fall in FEV_1 of at least 15% after exercise were entered into the study.

The children who fulfilled the entry criteria attended the laboratory on two more occasions, which were not less than four and not more than 10 days apart. On each occasion medication was withheld as before. FEV_1 was measured and provided this was within 15% of the previous baseline value the study proceeded.

Either 50 μg salmeterol or placebo were administered as aerosols via a large volume spacer device (Volumatic, Allen and Hanburys[19]). Exercise tests using the same settings as in the initial test and with the same measurements of heart rate and FEV_1 were done 1, 5, and 9 hours later.

ANALYSIS OF DATA

Group data was expressed as means and 95% confidence intervals (CI). Parametric analyses were used only when normal distribution of data had been established. The pretreatment values of FEV_1 were compared using the paired *t* test. Baseline FEV_1 before the initial exercise test and pretreatment FEV_1 on the two study days were compared using a two way analysis of variance (ANOVA) with patient and study day as factors. Factors influencing maximum fall in FEV_1 after exercise and change in FEV_1 after treatment were analysed by multiple regression analysis of patient, pretreatment FEV_1, treatment, treatment order, and time point after treatment. The maximum falls in FEV_1 after exercise at 1, 5, and 9 hours after salmeterol were compared with placebo using paired *t* tests, including the Bonferroni adjustment.[20] Two way ANOVA was used to compare the maximum falls after exercise 1, 5, and 9 hours after each treatment (salmeterol or placebo) with patient and time after treatment as factors. The change from baseline in values of FEV_1 before exercise on each study day and at each time point were compared using two way ANOVA. On the day salmeterol was given, FEV_1 before treatment and FEV_1 before each of the exercise tests were compared by two way ANOVA. Heart rate before treatment and before each of the exercise tests was analysed for treatment effect using two way ANOVA. For the placebo study day the same analyses were performed.

Table 1 Maximum percentage fall in FEV_1 after exercise

Patient No	*1 Hour*		*5 Hours*		*9 Hours*	
	Placebo	*Salmeterol*	*Placebo*	*Salmeterol*	*Placebo*	*Salmeterol*
1	40·6	−3·3	44·2	0·8	39·8	2·3
2	44·8	7·8	31·2	13·5	32·6	12·5
3	32·9	3·5	17·6	2·1	25·5	3·0
4	11·6	8·5	17·5	7·8	18·3	7·2
5	21·6	7·3	15·4	7·3	32·1	0·0
6	41·5	7·2	32·2	6·6	40·4	7·2
7	13·1	−2·2	1·0	0·9	17·8	1·7
8	36·1	4·6	38·8	3·8	44·5	5·4
9	20·8	−1·8	37·5	3·2	29·4	1·6
10	23·7	1·3	21·7	10·5	28·3	5·3
11	2·7	0·0	4·0	2·7	1·4	1·4
12	14·8	0·0	18·6	8·0	20·3	−3·0
13	16·3	1·6	15·2	1·6	14·7	3·6
Mean	24·6	2·7	22·7	5·3	26·6	3·4
Mean difference (95% CI)	22·0 (14·3 to 29·7)		17·4 (9·3 to 25·5)		22·8 (16·0 to 29·7)	

Patients

Thirteen children, five girls and eight boys, aged 8 to 15 (mean 12) years fulfilled the entry criteria and completed the study. All were taking an inhaled bronchodilator as required, two were also taking sodium cromoglycate, seven inhaled steroids, and one theophylline. The children remained well and free of respiratory tract infections or exacerbations of their asthma for the duration of the study.

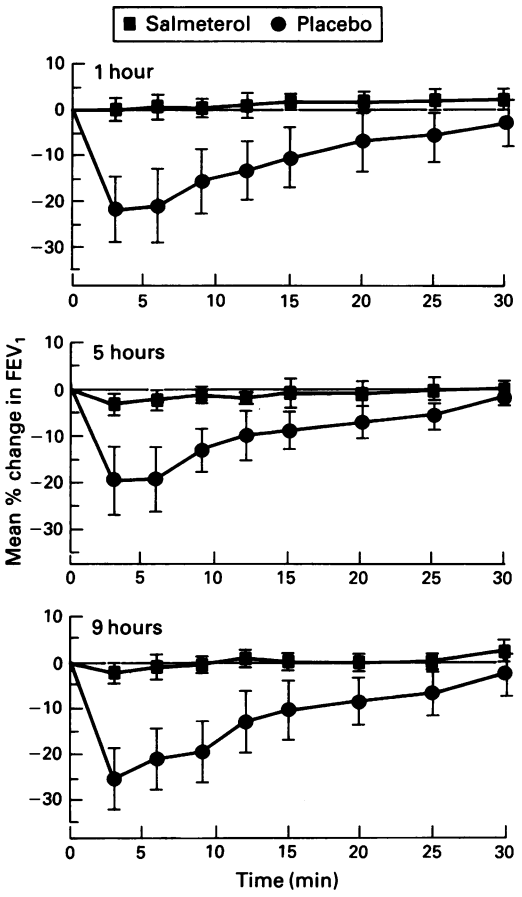
Results

Baseline values for FEV_1 at the first visit were from 66% to 104% of predicted (mean 87%). There was no difference between the pretreatment FEV_1 values for the two study days ($p=0·24$) and no difference between the initial values for FEV_1 on the three visits ($p>0·25$).

The only significant factors for fall in FEV_1 after exercise were treatment ($p<0·001$) and patient ($p<0·001$). When the children were treated with salmeterol they had a significantly smaller fall in FEV_1 after exercise at 1 hour ($p<0·0003$), at 5 hours ($p<0·0015$), and at 9 hours ($p<0·0003$) than when given placebo. After salmeterol there were no children who had a fall in FEV_1 of greater than 15% during exercise tests at 1, at 5 and at 9 hours. After placebo the number of children with a fall in FEV_1 of greater than 15% was 10 at 1 hour, 11 at 5 hours, and 12 at 9 hours (table 1). The degree and duration of bronchoconstriction after 1, 5, and 9 hours was very consistent on the day each child was given placebo ($p>0·1$). When salmeterol was given there was complete inhibition of bronchoconstriction at each time point with no diminution of effect over 9 hours ($p>0·05$; figure).

Multiple regression analysis showed the only significant factors for change in FEV_1 after treatment were treatment ($p<0·001$) and patient ($p<0·001$). Salmeterol caused a significant increase in FEV_1 before exercise at 1, 5, and 9 hours ($p<0·001$). This increase was similar before each exercise test ($p<0·25$). On the placebo study day there was no difference between the baseline and values for FEV_1 before exercise ($p>0·25$; table 2).

There was no difference between the heart rates before treatment and before exercise on the salmeterol study day ($p>0·05$) or the placebo study day ($p>0·25$). Mean heart rate before treatment on the salmeterol study day was 88·5 (CI 77·6 to 92·5). The mean heart rates



Change in FEV_1 after exercise. Bars show 95% CI.

(bpm) before exercise were 89·2 (CI 82·4 to 96·1) at 1 hour, 92·2 (CI 85·8 to 98·5) at 5 hours, and 95·2 (CI 89·8 to 100·7) at 9 hours. Mean heart rate before treatment on the placebo study day was 88·5 (CI 82·4 to 94·6). The mean heart rates before exercise were 85·1 (CI 77·6 to 92·5) at 1 hour, 89·1 (CI 82·8 to 95·3) at 5 hours, and 88·9 (CI 82·8 to 95·0) at 9 hours. No adverse effects were seen.

Discussion

Our results confirm that the technique of repeated exercise tests on a single study day is reproducible. The mean of the individual coefficient of variation for the maximal percent fall in FEV_1 after the three exercise tests on the placebo study day was 25·5%; this is similar to previous studies.[1 6 7] There was a placebo effect in some children. The maximal fall in FEV_1 was reduced by more than 15% in at least a third of the children after each of the exercise tests on the placebo study day (5/13 at 1 hour, 7/13 at 5 hours, and 7/13 at 9 hours). The effect of placebo on exercise induced asthma has been noted before.[17] In our study the effect on the group as a whole was small and analysis by two way ANOVA of the maximal fall in FEV_1 after the initial entry exercise test and after the three exercise tests on the placebo study day did not show a difference ($p>0·01$).

The duration of inhibition of exercise induced asthma in children by inhaled salmeterol xinafoate in this study (at least 9 hours) exceeds that reported in studies of other β_2 agonists. Though the exact mechanisms by which β_2 agonists protect against exercise induced asthma are unclear, it is not apparently related to their bronchodilator effect as bronchodilatation is still present at a time when there is no longer any protective effect against exercise induced asthma.[7 11 21] In our study bronchodilatation was present before each exercise test so it was not possible to exclude bronchodilatation as an alternative cause of the protection from exercise induced asthma. To resolve this question a study with exercise tests at later time points after treatment would be needed. Raised concentrations of inflammatory mediators have been demonstrated after exercise,[22] and inhibition of mediator release is a possible mechanism for the prevention of exercise induced asthma.[7 12 23] Salmeterol has been shown to block the early and late response to inhaled allergen, suggesting an effect extending beyond a protective action on airways smooth muscle.[16]

Tachycardia is a known side effect of β_2 agonists,[24] but in the dose administered there was no significant increase in heart rate before exercise after inhaled salmeterol (two way ANOVA $p>0·05$). Concern has been expressed recently about the regular use of β_2 agonists, particularly as a recent study has found regular use of inhaled fenoterol is associated with deterioration of asthma control.[25] Studies with salmeterol have not shown any deterioration of asthma control[26 27] so the effect observed with fenoterol may not apply to all β_2 agonists.[28] It is unlikely that concern over regular usage of β_2 agonists will apply to their intermittent use on days when vigorous exercise is anticipated.

Asthmatic children, even when receiving regular prophylaxis, may still need pretreatment with an inhaled β_2 agonist to inhibit exercise induced asthma.[6] The main disadvantage of current β_2 agonists is their short duration of action. As organised school sporting activities take place during the afternoon, prevention of exercise induced asthma during these activities relies on asthmatic children taking their treatment at school. A recent study of school teachers in London showed limited understanding of asthma, with only half answering that they should ensure that necessary drugs are taken before games. In addition only half of the teachers would allow asthmatic children to keep their medicines with them.[29] This may

Table 2 Percentage increase in FEV_1 before each exercise test (from pretreatment baseline)

Patient No	*1 Hour*		*5 Hours*		*9 Hours*	
	Placebo	*Salmeterol*	*Placebo*	*Salmeterol*	*Placebo*	*Salmeterol*
1	−0·0	16·5	9·0	20·3	9·0	23·1
2	15·9	39·6	0·0	35·9	7·7	39·6
3	1·8	7·5	10·3	2·7	1·2	6·9
4	8·8	30·1	7·6	25·2	13·2	19·0
5	−3·4	14·9	7·7	15·7	10·2	17·3
6	0·0	37·4	5·3	42·1	4·1	37·4
7	11·5	20·4	6·3	25·3	8·3	26·3
8	6·6	44·4	−19·2	39·1	−5·0	47·0
9	8·2	7·8	6·1	21·6	−6·1	21·6
10	−1·7	8·8	0·0	11·7	0·0	10·2
11	1·4	0·0	4·1	6·6	−4·1	1·4
12	10·4	4·4	7·4	10·2	5·9	−1·5
13	0·6	0·0	4·0	0·0	0·0	1·0
Mean	4·6	17·8	3·7	19·6	3·4	19·2
Mean difference (95% CI)	13·2 (4·6 to 21·8)		16·0 (4·9 to 27·1)		15·8 (5·9 to 25·6)	

compound the difficulties facing children who ought to be taking prophylaxis against exercise induced asthma before sport. Physical activities are useful to asthmatic children and appropriate prophylactic treatment by β adrenergic agents will usually permit full participation.[30] In addition efforts should be made to enhance the child's feelings of self worth and avoid feelings of being different from other children.[30]

A single dose of salmeterol xinafoate could be given by a parent in the morning on a day in which sporting activities were anticipated. This would avoid the need for the child to take or be given a dose before exercise. This would also remove any peer pressure attendant on their being seen to take an inhaler at school.

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